Replaced By Article 19

Patent Claims

1. A polypeptide variant with increased heparin-binding ability, **characterized in that**

   (i) added to the amino acid sequence of a polypeptide is at least one oligopeptide comprising the amino acid sequence $X_1X_2X_3X_4X_5X_6$; and/or

   (ii) inserted into the amino acid sequence of a polypeptide is at least one oligopeptide comprising the amino acid sequence $X_1X_2X_3X_4X_5X_6$; and/or

   (iii) at least one oligopeptide sequence naturally occurring within the amino acid sequence of a polypeptide is substituted by an oligopeptide comprising an amino acid sequence $X_1X_2X_3X_4X_5X_6$,

   wherein

   X_1 = K, R, or H;
   X_2 = K, R, or H;
   X_3 = K, R, H, or no amino acid;
   X_4 = not K, R, H, but any other amino acid;
   X_5 = not K, R, H, but any other or no amino acid;
   X_6 = not K, R, H, but any other or no amino acid (SEQ ID NO: 1),

   or

   X_1 = K, R, or H;
   X_2 = not K, R, H, but any other amino acid;
   X_3 = K, R, or H;
   X_4 = not K, R, H, but any other amino acid;

X_5 = not K, R, H, but any other or no amino acid;
X_6 = not K, R, H, but any other or no amino acid (SEQ ID NO: 2).

2. A polypeptide variant as recited in claim 1, characterized in that one to four copies of said oligopeptide are inserted at one to four positions within the polypeptide.

3. A polypeptide variant as recited in claim 1 or 2, characterized in said oligopeptide comprises amino acid sequence RKRA (SEQ ID NO: 3) or RKRAKHKQ (SEQ ID NO: 4).

4. A polypeptide variant as recited in any one of claims 1 to 3, characterized in said oligopeptide is added to the N-terminus and/or inserted into the N-terminal region, and/or substitutes a part of the N-terminal region.

5. A polypeptide variant as recited in any one of claims 1 to 4, characterized in that the amino acid sequence of said polypeptide variant further contains a sequence of relevance to recombinant expression at the N-terminus, said sequence of relevance to recombinant expression being M or MZ, where M stands for methionine and Z stands for one or more amino acids.

6. A polypeptide variant as recited in any one of claims 1 to 5, characterized in that said polypeptide variant further contains a His-tag.

7. A polypeptide variant as recited in any one of claims 1 to 6, characterized in that said polypeptide shows biological activity.

8. A polypeptide variant as recited in claim 7, characterized in that said polypeptide shows osteogenetic activity.

9. A polypeptid variant as recited in claim 7 or 8, **characterized in** that said polypeptide is selected from a hormone, cytokine, or a growth factor, or from a hormone, cytokine, growth factor that has been altered by addition, substitution, insertion, inversion, and/or deletion, where said polypeptide altered by addition substitution, insertion, inversion and/or deletion shows at least 10% of the biological activity of the unaltered polypeptide, and/or at least 50% homology to the unaltered polypeptide.

10. A polypeptide variant as recited in any one of claim 7 to 9, **characterized in** said polypeptide is selected from among members of the DVR family including the TGF-ß superfamily.

11. A polypeptide variant as recited in claim 10, **characterized in** that said polypeptide is BMP-2, BMP-4, BMP-5, BMP-6, BMP-7/OP-1, or BMP-8/OP-2.

12. A polypeptide variant as recited in claim 10 or 11, **characterized in** that said oligopeptide is inserted before the cysteine knot.

13. A polypeptide variant as recited in any one of claims 10 to 12, **characterized in** that said polypeptide variant has the amino acid sequence SEQ ID NO: 5 (T3) or SEQ ID NO:6 (T4).

14. A polypeptide variant as recited in any one of claims 1 to 13, **characterized in** that said polypeptide variant is a polymer, oligomer, or dimer of said polypeptide variant as recited in any one of claims 1 to 13.

15. A nucleic acid molecule, comprising a nucleic acid sequence encoding a polypeptide variant as recited in any one of claims 1 to 14.

16. A nucleic acid molecule as recited in claim 15, **charact rized in** that said nucleic acid s quence is derived from genomic DNA or cDNA, or is a synth tic DNA.

17. A nucleic acid molecule as recited in claim 15 or 16, further comprising a promoter suited to control expression, wherein said nucleic acid sequence encoding a polypeptide variant is under the control of said promoter.

18. A nucleic acid molecule as recited in any one of claims 15 to 17, wherein said nucleic acid molecule contains at least part of a vector.

19. Host cell, containing a nucleic acid molecule as recited in any one of claims 15 to 18, wherein said host cell is a prokaryotic or eukaryotic cell suitable for expression of said nucleic acid molecule.

20. A process for producing a polypeptide variant with increased heparin-binding ability as recited in any one of claims 1 to 14, comprising:
addition to the amino acid sequence of a polypeptide of at least one oligopeptide containing an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2; and/or
insertion into the amino acid sequence of a polypeptide of at least one oligopeptide containing an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2; and/or
substitution of at least one oligopeptide sequence naturally occurring within the amino acid sequence of a polypeptide by one oligopeptide containing an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2.

21. A process as recited in claim 20, **characterized in** that said process comprises a chemical and/or enzymatic synthesis process.

22. A process as recited in claim 20 or 21, **characterized in** that said process compris s gene technological processes.

23. A process as recited in any one of claims 20 to 22, **characterized in** that said process comprises:

a) *in vitro* mutagenesis of a nucleic acid encoding a polypeptide, so that
(i) to the nucleic acid encoding said polypeptide is added at least one nucleic acid encoding an oligopeptide containing an amino acid sequence that is selected from SEQ ID No.1 or SEQ ID No. 2; and/or
(ii) into the nucleic acid encoding said polypeptide is inserted at least on nucleic acid encoding an oligopeptide containing an amino acid sequence that is selected from SEQ ID No. 1 or SEQ ID No. 2; and/or
(iii) at least one nucleic acid sequence naturally occurring within the nucleic acid sequence encoding said polypeptide is substituted by a nucleic acid sequence encoding an oligopeptide containing an amino acid sequence selected from SEQ ID No.1 or SEQ ID No. 2;

b) cloning of the mutated nucleic acid into a suitable expression vector;

c) transformation/transfection of a suitable host cell with the expression vector obtained;

d) cultivation of said transformed/transfected host cell under conditions suitable for expression;

e) isolation, and if necessary renaturation, of the expressed polypeptide variant.

24. A process as recited in any one of claims 20 to 23, **characterized in** that said process is carried out within a prokaryotic host cell such as preferably *E. coli*.

25. A process as recit d in any one of claims 20 to 23, **characteriz d in** that said process is carried out within a ukaryotic cell, preferably a yeast, plant or ins ct cell, CHO or COS cell.

26. A pharmaceutical composition, comprising a polypeptide variant as recited in any one of claims 1 to 14 and, optionally, physiologically compatible additives.

27. Use of a polypeptide variant as recited in any one of claims 1 to 14 to stimulate osteogenesis or wound healing, or to treat inflammation or cancer.

28. A composition for osteoinduction, comprising a polypeptide variant as recited in any one of claims 1 to 14 and a carrier selected from among heparin, hydoxyapatite, hyaluronic acid, synthetic polymers, and collagen.

29. An osteoinductive matrix, **characterized in** that said matrix contains or is coated with heparin or heparin-like substances and polypeptide variants as recited in any one of claims 1 to 14 are adsorbed to said heparin or heparin-like substances.